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Cognitive Function Estimation in Children with Tuberous Sclerosis

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Abstract

Tuberous sclerosis (TSC) is a genetic disease characterized by cerebral structural abnormalities (such as cortical tubers, subependymal nodes and abnormal cerebral white matter) which are detected by means of neuroimaging methods (e.g., MRI). Typically, these events cause neurological complications (i.e., epilepsy).

Objective: cognitive function estimation in TSC children considering severity and nature of clinical course of the disease. 15 children with tuberous sclerosis (i.e., experimental group) and 46 children with normal development (i.e., control group) aged 6-16 years old underwent neuropsychological examination.

As a result, polymorphic disorders of higher mental functions were revealed in TSC children. Neuropsychological deficit ($p<0.05$) was detected. Namely, voluntary attention and memorization impairments were found in TSC children with normal development. Operational thinking disorders, immaturity of dynamic and kinesthetic movement basis, somatosensory gnosis, optical spatial or quasi-three-dimensional imaging, as well as insufficient oral/aural and semantical memorization were mentioned in TSC children with mental retardation. Regardless of mental development, TSC children demonstrate neurodynamic activity disorder ($p<0.05$) presented by slow task performance, increased exhaustability and attention fluctuation.

According to comparison between research findings and clinical course data, severity of cognitive disorders substantially depends on epilepsy onset age because early onset results in more severe developmental disorder ($p<0.05$).

Since tuberous sclerosis is a dynamic disease with new potential symptoms arising over a lifetime, neuropsychological testing will provide timely mental status qualification and development of corrective actions to activate cognitive activity of a child.

Keywords: tuberous sclerosis, children, higher mental function (HMF) developmental disorders.

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1. Introduction

According to the Ministry of Healthcare of the Russian Federation, tuberous sclerosis is on the list of rare (orphan) diseases falling into congenital malformations, deformations and chromosomal abnormalities (ICD-10 code: Q85) since 2014. Neonatal prevalence varies from 1:5800 to 1:10000. Official international genetic symbol of tuberous sclerosis is TSC (tuberous sclerosis complex) [1].

At 7-20 weeks of intrauterine development tuberous sclerosis genetic mutations influence on nervous system precursors. In this case, interrupted cell separation and abnormal cell differentiation, as well as disordered control of cellular size and migration may be detected. As a result, multiple benign tumors in various organs and tissues along with structural cerebral abnormalities (such as cortical tubers, subependymal nodes and abnormal white cerebral matter) revealed by means of neuroimaging methods (i.e., MRI) are formed [2].

According to research findings, signs of central nervous system damage (i.e., epilepsy, cognitive and behavioral disorders, autism) are mentioned in 85% of TSC children. Epileptic episodes (i.e., manifest symptoms of the disease) are observed in 75-92% of patients. Autism and attention deficit and hyperactivity disorder (incidence > 50 %) are the most common behavioral disorders in TSC children. Cognitive deficit associated with tuberous sclerosis varies widely from mild intellectual incapacity to severe mental retardation [3, 4].

In spite of various cerebral disorders, tuberous sclerosis is characterized by their variability (i.e., new symptoms may appear during growing-up) resulting in essential medical and psychological follow-up. In particular, it's a topical issue to determine developmental and educational prognosis, as well as to develop an approach to psychological corrective aid. This begs the question about timeliness of this assistance because the earliest assistance will provide the best result.

Evaluation of cognitive functions in children with tuberous sclerosis should be analyzed in the context of combined multidisciplinary approach integrating neuropsychological findings and psychophysiological cerebral testing results (i.e., MRI - magnetic resonance imaging, EEG - electroencephalogram).

2. Methodology

The research included methods listed below:

1. clinical neurological methods (history and clinical course of disease);
2. psychophysiological cerebral testing (MRI, EEG);
3. methodological complex of general neuropsychological testing developed by A.R. Luria and adapted for children. Diagnostic schedule included an interview and higher mental function testing by means of several neuropsychological tests (such as kinesthetic, spatial and dynamic praxis, auditory-motor coordination, visual gnosis, tactile gnosis, quasi-three-dimensional imaging, oral/aural memorization, picture tests and thinking) [5, 6].

Qualitative and quantitative (scored) evaluation of concerned functional parameters was based on testing results. Qualitative evaluation was performed in the context of structural-functional conception, developed by A.R. Luria, dealing with three cerebral blocks each of which provides a specific component of mental activity in the system of cerebral structure [5, 6].

Quantitative evaluation considered age-related standard results of several tests (Mikadze Yu.V., Akhutina T.V., Chelysheva, M. V.) [7–9]. Intensity of any disorders revealed during tests was expressed as demerit points. In particular, 0 scores - errorless test performance; 1 score - mild disorders, potential individual error correction (<30% of errors); 2 scores - moderate disorders, potential error correction and task performance following researcher's prompts (30-70% of errors); 3 scores - frank disorders (70-100% of errors).

In order to process (SPSS software 17.0) and analyze research findings, mathematical statistical methods (i.e., Mann-Whitney test; $p < 0.05$) were used to perform statistical analysis.

Experimental population included 15 children aged 6-16 years old with tuberous sclerosis (TSC) who were treated in the Department of Psychoneurology in Vel'tishchev Scientific Research Clinical Institute of Pediatrics of Federal State Budgetary Educational Institution of Higher Education Pirogov Russian National Research Medical University of the Ministry of Healthcare of the Russian Federation. Children with tuberous sclerosis (TSC) were enrolled in the experimental group. Control group of neuropsychological analysis consisted of 46 children aged 6-16 years old with normal mental development visiting general educational institutions (i.e., a childcare center or a school). Children with normal development were enrolled in the control group. Mean demerit points were calculated for each group.

3. Results

In order to evaluate results, TSC children enrolled in the experimental group were divided into 2 age subgroups. The first one included patients aged 6-10 years old (average age: +/- 8 years) and the second one included children aged 15-16 years old). Along with this, results of diagnostic tests performed by TSC children pursuing principal educational program and adapted corrective program (remedial school) were of interest in each group. Controls were also divided into 2 age subgroups (i.e., children aged 6-10 and 15-16 years old, respectively).

Subgroup division considered age-related dynamics of higher mental function formation and sample size.

Age group-based characterization of TSC children considering severity of the disease and mode of study is presented in Tables 1-2.

Table 1: Age-based distribution of TSC children.

Age of subjects	Number of subjects			
	M	F	Total number	
	abs.	abs.	abs.	%
TSC group				
6-10 years	3	6	9	60%
15-16 years	3	3	6	40%
Total	6	9	15	100%

Table 2: Distribution of TSC children considering severity of the disease.

Development	Mode of study	Number of subjects	
		abs.	%
6-10 years			
Normal development	general education childcare center and school	4	26%
Mental retardation	remedial school	5	34%
15-16 years			
Normal development	general education school	2	14%
Mental retardation	remedial school	4	26%
Total		15	100%

Neuropsychological findings are presented by Figures 1-2. Disorders of higher mental functions were evaluated by comparison between number of demerit points (i.e., means calculated for age subgroups) resulted from several tests performed by TSC children and controls.

Neuropsychological deficit was detected in TSC children:

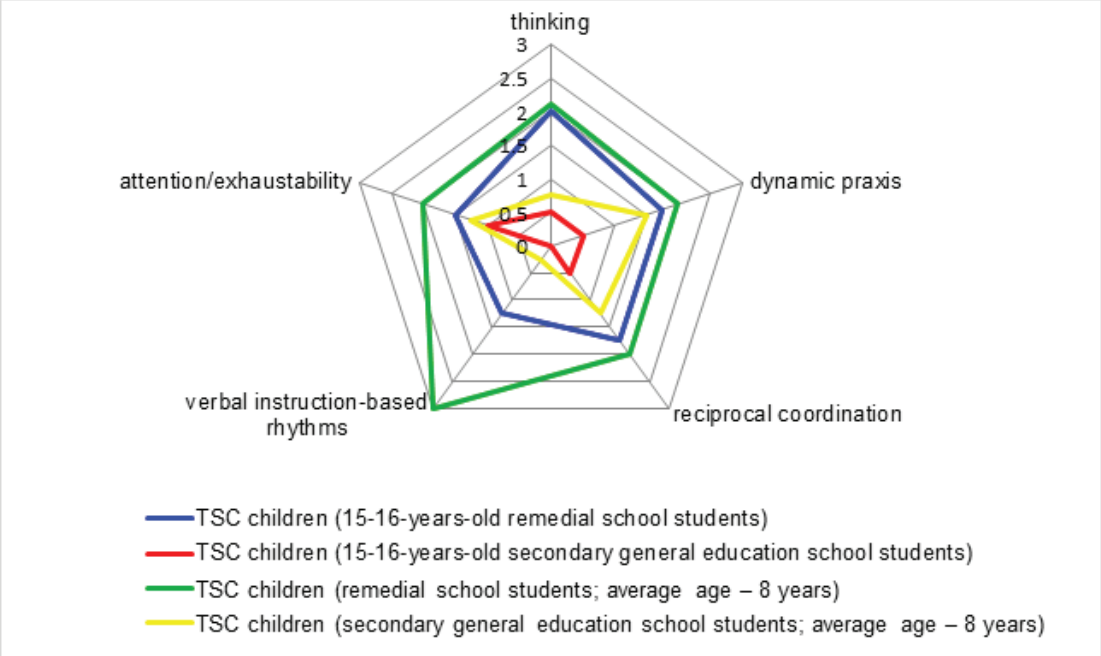

Figure 1: Evaluation of disorders of higher mental functions in TSC children based on neuropsychological tests used to analyze functioning of the cerebral blocks I and III (on axes - results in points).

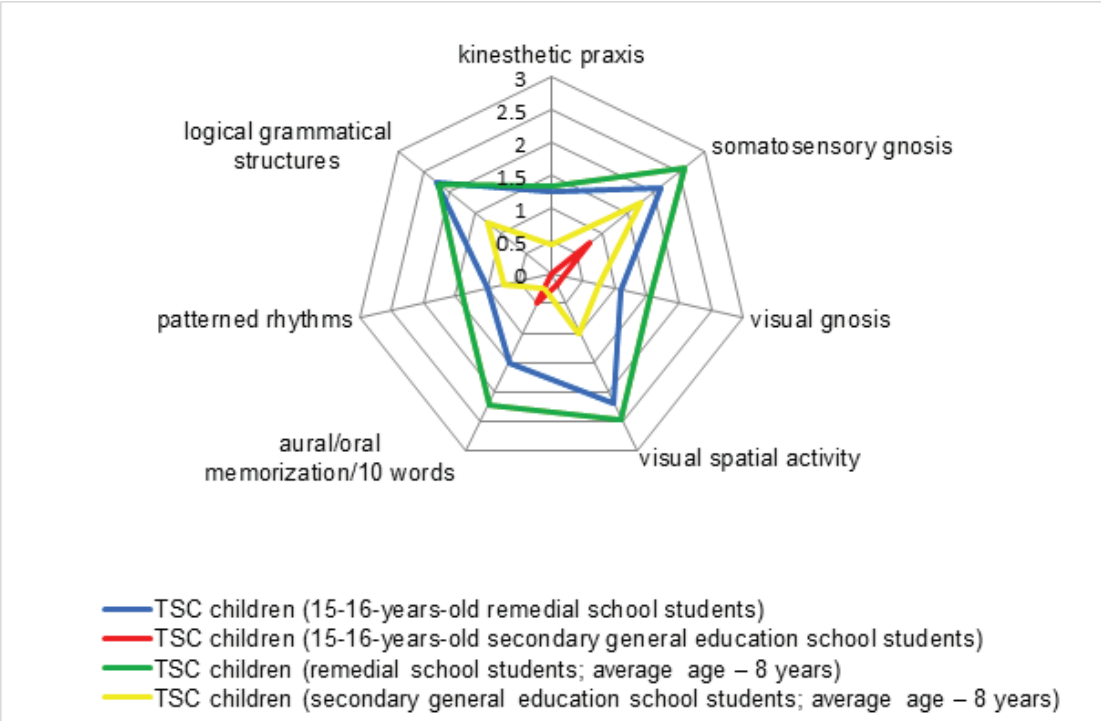

Figure 2: Evaluation disorders of higher mental functions in TSC children based on neuropsychological tests used to analyze functioning of the cerebral block II (on axes - results in points).

1. *secondary general education school students (general education schools)* - insufficient neurodynamic activity parameters (exhaustability, slower task performance); insufficient kinesthetic basis of movements and actions, impaired dynamic praxis and aural/oral memorization.

2. *remedial school students* - impaired neurodynamic activity; disordered operational thinking (decreased generalization, logical grammatical structure misunderstanding, complicated performance of mathematical operations and actions); insufficiency of dynamic praxis, dermatic kinesthetic sensitivity, optical spatial imaging and oral/aural memorization.

3.1. Evaluation of neuropsychological diagnostic findings in TSC children considering epilepsy onset age

A concomitant diagnosis (i.e., symptomatic focal epilepsy) was mentioned in clinical presentation of all the TSC children. Epileptic episode manifestation onset in the experimental group was distributed as follows: 9 patients with early epileptic manifestation (age < 3 years); 4 patients with epileptic manifestation between 3-7 years old; 2 patients with epileptic manifestation above 7 years old.

According to this sample, clinical data compared with neuropsychological findings demonstrated significant relationship between epileptic onset age and cognitive function development. Children with late epileptic onset age demonstrated milder HMF disorders (i.e., lower demerit points). Thus, earlier onset results in more severe developmental disorder ($p<0.05$).

Evaluation of mental functional disorders in children with tuberous sclerosis considering epileptic onset age is presented by Figure 3.

The figure clearly demonstrates a known thesis about specific influence of damage onset on mental functional development in the context of ontogenesis. Namely, early abnormal impact on a developing brain leads to more severe mental developmental disorder.

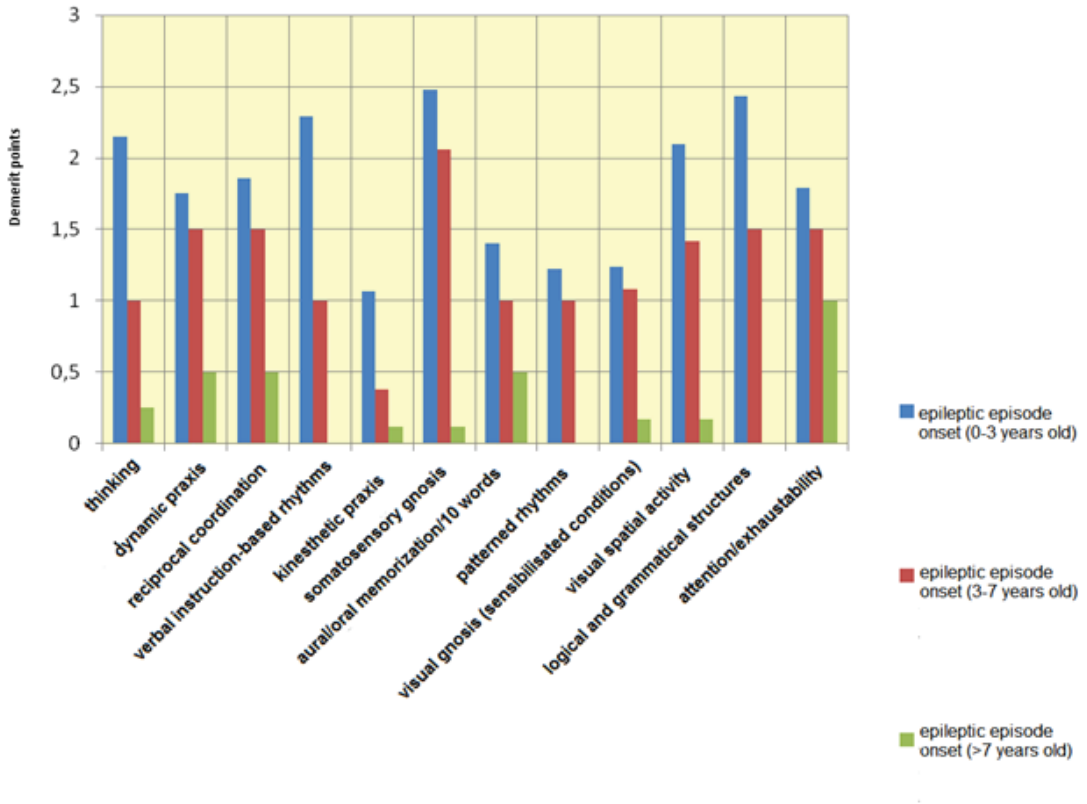

Figure 3: Evaluation of mental functional disorders in TSC children considering epileptic onset age.

3.2. Evaluation of neuropsychological diagnostic findings in TSC children considering structural cerebral disorders

TSC-associated pathomorphological cerebral alterations affect both cortical and deep subcortical structures (i.e., structures forming lateral ventricular walls such as caudate nucleus, hippocampus, corpus callosum, superior thalamic surface, nodules/astrocytomas of foramina of Monro).

According to MRI findings, cortical and subcortical tubers (100%), subependymal nodules (SEN), astrocytomas of foramina of Monro (87%) and white matter alterations (40%) were detected in the experimental group.

It is interesting to note variable cerebral tuberous spread varying from solitary cortical tubers to multiple cortical and subcortical lesions in the experimental TSC group. Correspondence between intensity of anatomical cerebral pathology and mental development in TSC children is presented in Table 3.

Multiple tubers localized in cortical and subcortical cerebral regions and the foramen of Monro rather clearly influence on severity of mental retardation.

However, tuberous number is not a definite marker of a cognitive disorder. According to our observations in the experimental TSC group, multiple tubers may provide no

Table 3: Relationship between structural cerebral abnormalities and mental development in TSC children expressed as a percentage of number of children in the group.

MRI-based structural cerebral abnormality intensity	Mental development intensity	
	mental retardation (N=9)	nominally normal development (N=6)
cortical and subcortical tubers		
solitary cortical and subcortical tubers	0%	50%
multiple cortical and subcortical tubers	100%	50%
cortical and subcortical tuberous dimension	< 39 mm	< 45 mm
lateral ventricular (LV) subependymal nodules		
subependymal nodules	100%	67%
lateral ventricular astrocytoma	11%	33%
LV subependymal nodule dimension	< 12 mm	< 7 mm
nodules/astrocytomas in the foramen of Monro		
nodules/astrocytomas in the foramen of Monro (expressed as percentage of number of children in the group)	78%	16%
dimension of nodules/astrocytomas in the foramen of Monro	< 14 mm	< 3 mm
white matter alterations	67%	33%

negative impact on cognitive functions. For example, according to MRI findings, 15-years-old Lisa I. has cortical tubers (max. dimension - 45*18 mm; calcified area is seen in the left parietal lobe) in convexital, medial and basal surfaces of the great hemispheres, subependymal nodes (<4 mm) localized on lateral walls of lateral ventricles, a lesion (7*3*7 mm) located leftward to the foramen of Monro and white matter alterations. Indeed, the patient demonstrated generally preserved intellect pursuing general education program.

Qualitative evaluation of cognitive functions in TSC children was performed during neuropsychological (syndrome) analysis of HMF disorders along with integration of neuroimaging findings (Table 4).

Neuropsychological symptoms in TSC children indicated dysfunction of several cerebral structures.

It's important to stress combined nature of neuropsychological syndromes in TSC children. Namely, primary disease is complicated by both cortical and subcortical syndromes enhancing cognitive and behavioral disorders.

Table 4: Cognitive disorders in TSC children considering cerebral damage topography.

TSC-associated cerebral damage topography	Cognitive disorder Basic symptoms	Neuropsychological symptoms
Structures forming lateral ventricular walls: Deep subcortical structures of the great hemispheres: caudate nucleus (basal ganglia), lateral ventricles. Limbic structures (corpus callosum, hippocampus). Diencephalic structures (superior thalamic surface) Foramen of Monro	**neurodynamic disorders of higher mental functions** (impaired voluntary attention, slower task performance, exhaustability, distractibility during task performance); **interhemispheric interaction deficiency** (insufficient performance of kinesthetic, dynamic and spatial praxis, complicated reciprocal coordination); **short-term aural/oral memory disorders** which are mainly observed in delayed component (i.e., increased memory trace inhibitability); **emotional disorders:** emotional instability, excitability, affective response.	Neuropsychological syndromes associated with deep cerebral subcortical structural damage
Mediobasal cortical regions of frontal and temporal lobes**/**cortical regions of non-specific system.	**impaired aural/oral memory** (literal paraphasia, decreased recitation); **voluntary attention deficit** (complicated concentration during task performance).	Neuropsychological syndromes associated with cerebral medial non-specific structural damage.
Anterior and posterior cerebral cortical regions	**impaired operational thinking** (decreased generalization, complicated understanding of picture sense); **insufficient dynamic praxis** (complicated/impossible achievement and retention of locomotor programme, perseveration); **insufficiency of kinesthetic movement basis, somatosensory gnosis, optical spatial and quasi-three-dimensional imaging.**	Neuropsychological syndromes associated with cortical damage of great hemispheres

4. Discussion

Research analysis revealed specific features of mental developmental disorders associated with tuberculous sclerosis. In particular, this means their wide variability from normal development to mental retardation of various severity complicated by behavioral deviations. Our findings correspond with data reported by foreign authors indicating inhomogeneous cognitive defect associated with the disease [10–12].

First of all, difficult mental ill-being presentation in the setting of tuberous sclerosis is related to early cerebral organic lesion leading to altered functional interaction between cerebral structures and, respectively, to another consequence and time of mental function maturing process. Life-long course of primary disease is characterized by instability of cerebral structural abnormalities and subsequent neurological complications causing additional difficulties in individual mental development.

5. Conclusions

The research broadens a concept of cognitive developmental features in children with tuberous sclerosis.

1. According to our findings, cerebral structural alterations observed in children with tuberous sclerosis:
2. *lead to cognitive disorders of various intensity, as well as emotional and behavioral disorders;*
3. *cause clinical symptoms and, respectively, neuropsychological syndromes.*
4. Neuropsychological syndromes associated with deep cerebral subcortical structural damage detected in all the TSC children are leading ones in the setting of this pathology.
5. Analysis of relationship between epileptic onset age and intensity of TSC-associated HMF disorders revealed significant influence of epileptic onset age on nature of cognitive disorders (earlier onset causes more severe developmental disorder; $p<0.05$).
6. The most severe behavioral and emotional disorders were mentioned in TSC children with combined damage of cortical and deep cerebral structures along with early epileptic onset.
7. Timely qualification of mental status of a TSC child must be performed to arrange corrective psychological educational and social aid. Also, it can be one more marker of severity deterioration.
8. Neuropsychological method to evaluate HMF status developed by A.R. Luria is an appropriate and informative technique to examine children with genetic syndromes.

The research revealed prognostically favorable and unfavorable parameters to develop cognitive functions in the setting of TSC.

Favorable factors:

1. absence or late onset of epileptic episodes (age > 3 years old);
2. small solitary cerebral tubers;
3. effective anticonvulsant therapy;

4. positive response to cognitive activity stimulation;
5. parental involvement in child's development.

Unfavorable factors:

1. early onset of epileptic episodes (< 1 year old);
2. drug resistance to anticonvulsant therapy
3. large multiple cerebral tubers;
4. autistic manifestations;
5. significant exhaustability of mental processes, weak initiative for cognitive activity;
6. educational neglect and social alienation of a child.

Since tuberous sclerosis is a dynamic disease, in order to minimize sequlae of new TSC symptoms, psychological diagnosis should be done along with regular clinical examination to detect current mental developmental disorders and to choose timely optimal corrective aid corresponding with the profile of detected disorders.

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